LETTER TO THE EDITOR

Omalizumab prevents anaphylactoid reactions to mRNA COVID-19 vaccine

Dear Editor,

Within the first days of initiating mass vaccination with the novel COVID-19 vaccines several anaphylactic reactions have been reported.[1] We present two cases experiencing angioedema with or without urticarial rash after the first dose of the mRNA-1273 vaccine. Both patients tolerated the second vaccination after a pretreatment with the anti-IgE antibody omalizumab.

The first patient, a 27 years old woman with no known allergies, developed dyspnoea, throat tightness, lip and tongue swelling, and flushing within the first hour after administration of the first vaccination. After treatment with intravenous antihistamines and glucocorticoids, the symptoms resolved. The second case, a 31 years old woman, developed an urticarial rash and subsequently a swelling of tongue and upper eye lids 10 days after receiving the first dose of the vaccine (Fig. 1). The symptoms reoccurred during the period of 9 days but resolved after 7 days of treatment with oral glucocorticoids as well as oral antihistamines. The patient reported on no other allergies apart from a type IV-sensitization to nickel.

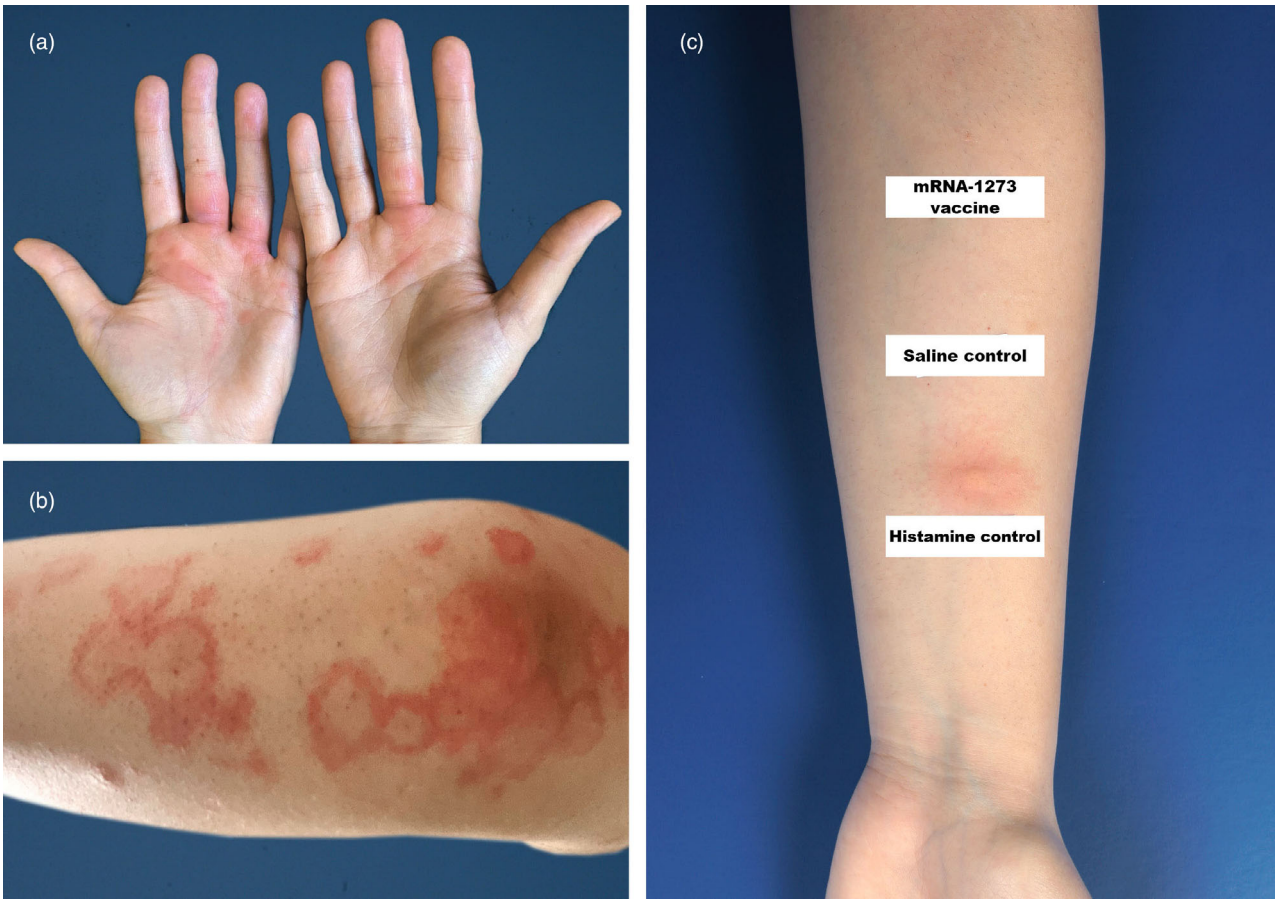

Figure 1 Urticarial rash following mRNA-1273 vaccination and skin prick test with mRNA-1273 vaccine. Urticarial skin lesions in patient #2 10 days after the first vaccination (a, b). Skin prick test in patient #2 showing negative results to mRNA-1273 vaccine with saline being used as negative control and histamine as positive control (c).

Table 1 Two patients developing anaphylactoid reactions after mRNA-1273 vaccination and receiving omalizumab prior to second dose

	Patient #1	Patient #2
Age in years	27	31
Sex	Female	Female
History of hypersensitivity	None	Type IV (nickel)
Time to systemic reaction after 1st dose	1 h	10 days
Symptoms	AE of lips and tongue incl. dyspnoea, flush	Urticarial rash with subsequent AE of tongue and upper lids
Treatment	i.v. CS and AH	Topical and oral CS, oral AH
Serology: total IgE, specific IgE to aeroallergens, tryptase levels (Immuno-CAP FEIA, Thermo Fisher Scientific Inc., Waltham, MA, USA)	NAD	NAD
Skin prick test (after suff. washout period)	Negative for mRNA-1273	Negative for mRNA-1273
BAT (mRNA-1273, PEG 2000, DMG PEG 2000; Bühlmann Laboratories AG, Schönenbuch, Switzerland)	Negative	Negative
Pretreatment with omalizumab in days to 2nd dose	2	7
Symptoms after 2nd dose	None	Solely localized urticaria after 8 days
SARS-CoV-2 nucleocapsid-specific IgG after 2nd dose	Negative	Negative
SARS-CoV-2 spike-specific IgG after 2nd dose	>384.00 BAU/mL	>384.00 BAU/mL
Neutralization titre after 2nd dose	80	320

Two patients who developed AE/AE with urticaria after first dose of mRNA-1273 and subsequently received pretreatment with omalizumab to prevent a possible anaphylactoid reaction listed with relevant clinical parameters. Antibody titre tests were performed to evaluate efficacy of mRNA-1273 vaccination: Patient sera were tested for SARS-CoV-2 nucleocapsid-specific IgG using SARS-CoV-2 IgG chemiluminescent microparticle immunoassay from Abbott performed on an ARCHITECT i2000 SR. Euroimmun Anti-SARS-CoV-2-QuantiVac-ELISA was used to measure IgG levels against SARS-CoV-2 spike S1 after the second vaccination. Neutralizing antibody titres were tested using an in-house serial dilution endpoint neutralization test performed under BSL-3 safety conditions.

AE, angioedema; AH, antihistamines; BAT, basophil activation test; CS, corticosteroids; DMG, dimyristoyl glycerol; i.v, intravenous; IgE, immunoglobulin E; NAD, no abnormality detected; PEG, polyethylene glycol.

In both patients, serological quantifications of total IgE, specific IgE to aeroallergens and tryptase levels revealed no hints of pre-existing type I-sensitizations or mast cell activation disorders (Table 1).

After a washout period of >14 days upon cessation of systemic anti-allergic treatments, skin prick tests using residuals of the mRNA-1273 vaccine displayed no positive response (Fig. 1). In addition, flow-assisted basophil activation assays determining CD63 expression showed no sensitizations neither to polyethylene glycol (PEG) nor to the mRNA-1273 vaccine (Table 1).

Thus, we found no evidence of pre-existing or newly acquired hypersensitivities to the mRNA-1273 vaccine or its components explaining the reactions in these cases. Hence, the immunological mechanisms behind the anaphylactoid reactions remain unclear. Acute allergic reactions to the novel mRNA COVID-19 vaccines have been described based on self-reports.[2] However, so far no type I-sensitization has been proven. Several publications reported on the efficacy of omalizumab, a recombinant humanized monoclonal anti-IgE antibody, in preventing hypersensitivity reactions even in cases without known triggers.[3]

Against this background, both patients were pretreated with a single dose of 300 mg omalizumab 2 and 7 days, respectively, prior to the second vaccination. Neither patient experienced angiooedema or urticarial rashes as immediate reactions after the second dose of the vaccine. The second patient showed a delayed reaction with fever and subsequent development of urticaria 8 days following the vaccination. However, this time the rash was by far less severe and thus no treatment with systemic glucocorticoids was required. Based on the clinical course and allergologic examinations, one could argue that the urticaria in the second case was most likely triggered by the delayed reactogenicity symptoms the patient experienced after the vaccination. Further, McMahon *et al.*[4] reported on urticarial rashes showing low second-dose recurrences. Hence, we cannot rule out that our second patient would have experienced less symptoms even without pretreatment with omalizumab.

To exclude any negative effect of omalizumab on the efficacy of the vaccination, the patients were tested for antibody titres: both exhibited high SARS-CoV-2 spike protein-specific antibody titres related to the vaccination (>384.00 BAU/mL on Euroimmun Anti-SARS-CoV-2-QuantiVac-ELISA) as well as moderate to high SARS-CoV-2 neutralizing antibody titres of 1 : 80 and 1 : 320, respectively, as determined by a serial dilution endpoint test in Vero cells (Table 1). Both patients were tested for SARS-CoV-2 nucleocapsid protein-specific antibodies beforehand using the SARS-CoV-2 IgG chemiluminescence microparticle immunoassay from Abbott to exclude an undetected infection prior to the vaccination.

Our two cases indicate that pretreatment with omalizumab could be a way of ensuring a safe and effective vaccination even

after experiencing anaphylactoid reactions following the initial dose of a COVID-19 vaccine.

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The patients in this manuscript have given written informed consent to publication of their case details.

Conflict of interest

SM reports personal fees and/or grants from Novartis, LEO Pharma, Almirall, AbbVie, Sanofi, UCB, Eli Lilly, Janssen Cilag, Milan and Pfizer, and BH reports personal fees and/or grants from Novartis, LEO Pharma, AbbVie, Sanofi, UCB, Eli Lilly, Janssen Cilag, Union Pharma and Pfizer. All COI are outside the present work. AS, SS, LM, OA and PA did not report any COI.

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